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Soft Tissue Manipulation: A Powerful Form of Mechanotherapy

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Abstract

This short review provides an important perspective on soft tissue manipulation/mobilization (STM) as a powerful and direct form of mechanotherapy, which has significant implications in physical rehabilitation, disease prevention and health promotions. STM, e.g. therapeutic massage, whether administered by hand alone or with a rigid device, is a type of manual therapy frequently used by clinicians worldwide to address common musculoskeletal pain disorders. It is a type of mechanotherapy which applies non-invasive mechanical stimuli to the surface of the body so as to influence molecular, cell and tissue structure and function via mechanotransduction, utimately leading to improved clinical outcomes. A brief overview of mechanotransduction is provided, with a focus on the ECM-integrin-cytoskeleton pathway, and the impact of STM mechanical stimulus on different tissue types are considered in this article. Ongoing research is suggested to further validate STM as a viable, cost-effective treatment option in an aging population and the clinical relevance of STM is discussed. STM intervention should be approached as a prescription, a targeted and precise form of mechanotherapy in which optimal dose pressures and frequencies are delivered to achieve desired outcomes and advance the field of soft tissue manual therapies.

Keywords: Soft tissue manipulation; Soft tissue mobilization; Massage; Mechanotherapy; Manual therapy; Physical therapy; Rehabilitation

Introduction

Musculoskeletal (MS) conditions are common and costly, occurring throughout the lifespan and involving most tissues types [1,2]. Manual therapy approaches are frequently used by clinicians to address these and other disorders [3]. In fact, one study found 87% of physical therapists use manual therapy on a daily basis [4]. Soft tissue manipulation/mobilization (STM) (e.g. therapeutic massage) is a type of manual therapy administered by hand alone or with a rigid device [5]. Instrument-assisted soft tissue mobilization (IASTM) is a type of STM that uses rigid devices to deliver specifically directed, targeted forces to the tissue [6]. Although STM is an ancient intervention with demonstrated positive effects, much remains to be understood about its underlying mechanobiology [7,8]. In essence, STM is a form of mechanotherapy, and understanding it as such may enhance its application and optimize treatment outcomes.

Mechanotherapy may be defined fundamentally as any intervention that uses mechanical stimuli to affect a biological change via mechanotransduction processes with an end goal to improve function [9,10]. Mechanotransductive pathways convert mechanical stimuli applied to the body into a cellular, molecular, and tissue responses [11-14]. Virtually all cells are mechanosensitive to their surrounding environment, in that physical forces, e.g. tension, compression, shear, hydrostatic pressure, fluid shear and vibration, play a role in the organization, growth, remodeling, maturation and function of tissues, and ultimately, the organism [15]. Most physical therapeutics employ mechanical forces to affect a desired change, including exercise [9], pulsed ultrasound [16], vibration [17], and as suggested in this perspective, manual therapies. Indeed, STM integrates most forms of mechanical stimuli that can directly influence molecular pathways, cellular response, tissue structure and function and healing, repair and regeneration [18]. The purpose of this short review is to provide a unique perspective on STM as a powerful form of mechanotherapy, i.e. soft tissue mechanotherapy, which is available to clinicians and patients worldwide. A brief overview of mechanotransduction mechanisms and the impact of STM mechanical stimulus on different tissue types will be considered.

Mechanotransduction Overview

Cells have the ability to sense changes in their environment (mechanosensation), including compliance of the extraracellular matrix, and to transduce these changes into biochemical signals (mechanotransduction). This ability is critical to the development, differentiation, function and survival of the cells, tissue and ultimately, the organism [11,12]. Here in lies the power of STM, as an important form of mechanotherapy, to positively affect the function and well-being of the whole individual. Most STM approaches possess a common denominator in that they exert targeted physical forces on the soft tissue that may be detected and converted into a signal with downstream biophysiological effects.

The concept of mechanical forces stimulating load-signaling pathways which affect a biological change is not new. Wolff's law [19] predicted that remodeling of bone occurs in response to physical stresses. This model led later to a concept that bone is deposited in sites subjected to stress and reabsorbed from sites with minimal stress and asserts mechanical stress helps orchestrate the architecture of bone [20]. The piezoelectric effect was used to explain this relationship between the structure and function in bone. This effect is described as the ability of some materials to generate an electric potential in response to applied mechanical stress. Davis' law is the connective tissue corollary of Wolff's law that describes how soft tissue models along imposed demands [20]. Buckminster Fuller, an architect, first introduced the concept of tensegrity in 1916, which offers a corollary

for a model of cell architecture that helps explain how the mechanical behavior of the cell emerges from physical interactions between its environment and among different molecular filament systems forming the cytoskeleton and the nucleus [21]. The model contends cell tensile elements (actin filaments) impose a pre-stress on cells that is countered by compression-resistive elements (microtubules) [14,22,23]. The mechanostat theory (Frost) contributed important health implications by suggesting there is a window of optimal load for signaling a therapeutic physiological response [24]. The concept of mechanotransduction evolved from these theories and may be defined as the processes whereby a mechanical stimulus is converted into biochemical responses that affect cellular and tissue functions [25,26]. It has been implicated as a mechanism for the treatment effects of other physical therapeutic modalities such as low intensity pulsed ultrasound in bone [27] and ligament healing [28]; acupuncture [29-31]; therapeutic exercise [1] in tendon, muscle [32], and bone [33,34]. Mechanotransduction is undoubtedly an underlying mechanism for the effects of STM. ·

An in depth discussion on mechanotransduction is beyond the scope of this perspective; however, the reader is referred to more in depth reviews [11-14,35,36]. To briefly summarize, it involves a cell-mediated process including intracellular and extra-cellular signaling, cell-matrix and cell-to-cell interactions and secretion of autocrine and paracrine factors. The extracellular matrix (ECM) is primarily composed of fibrous proteins, proteoglycans and water. Collagen is the most ubiquitous ECM protein. The ECM provides a structural architecture and milieu in which cells can function to maintain homestasis, promote tissue growth and reorganization, and support healing and repair. Fibroblasts serve as the primary mechanosensing cells in connective tissue. The ECM both influences and is influenced by microscopic molecular and macroscopic environmental cues in a reciprocal, structural and functional relationship leading to heterogeneous connective tissue organization.

Different pathways mediate mechanotransduction in sophisticated, integrated and complex manners, but the transmembrane ECM-integrin-cytoskeletal signaling axis, which pre-stresses the cell and connects the ECM to the intracellular cytoskeleton, is likely a prominent pathway stimulated by STM. Figure 1 depicts a schematic illustration of the integrin-mediated mechanotransduction pathway whereby an IASTM device is used to apply a force through the skin's surface to affect change. In a domino manner, the device (or hand) exerts a force on the skin's surface, which deforms the ECM that is linked to the cell membrane of the target tissue cell. This connection allows the force to travel through cell membrane integrins which are connected externally to the ECM and internally to intracellular linker proteins. The STM forces are then transferred to the cytoskeletal filaments which are physically tethered structurally to the nuclear lamina via connection to complex proteins. These in turn are structurally linked to the chromatin (nuclear DNA) inside the nucleus, whose deformation may subsequently alter gene activity, transcription and protein synthesis. Thus, mechanocoupling of the interior and exterior of the cell through ECM-cytoskeletal-nuclear connections allows for nuclear deformation and re-organization in response to internal and external stimuli. The process of change in the chromatin produces a change in the biochemical products of the cell. The biochemical products may then communicate with another cell (paracrine effects) or itself (autocrine effects) via signal transduction to cause the effector cell (self or other) to respond. The response of the effector cell affects a change in tissue structure/function that can ultimately affect the ability of the body to function in a pain-free manner [35,36].

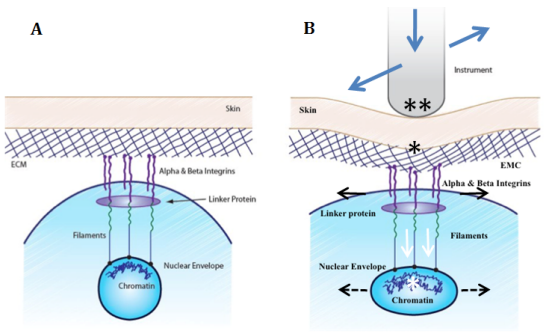

Figure 1: Mechanotransduction of soft tissue mechanotherapy forces. This schematic drawing illustrates a simplified scenario from a clinical perspective of a possible direct signaling cascade along the ECM-integrin-cytoskeleton axis in response to a form of IASTM. **A)** Represents unstimulated soft tissue at rest. **B)** The mechanotransduction cascade is initiated during STM when a rigid instrument (IASTM) (double black **) is used to apply a mechanical load (stress) to the body surface in different directions (blue arrows) to provide mechanical stimuli (e.g. compression, stretch, shear) which generates deformations (strain) in the ECM of underlying soft tissue (*). The physical force is then transduced by integrins in the plasmalemma into an intracellular response (? ?). The signal is subsequently transmitted through the cytoskeleton filaments (white arrows) to the nucleolemma (broken black arrows), that is structurally tethered to the nuclear DNA in the form of chromatin (white*), which is subsequently deformed leading to possible gene expression that may result in increased mRNA levels, translation and protein synthesis, ultimately culminating in altered cell function and tissue-level responses that can affect the organism as a whole.

STM mechanotherapy can have direct and rapid effects on tissue due to nearly instantaneous propagation of the mechanical signaling cascade and synthesis from the ECM-integrin-cytoskeletal and other signaling pathways [12]. Mechanosensation and mechanotransduction mechanisms allow for sophisticated integration of forces imparted through the body's surface, including load magnitude, frequency, rate, direction and duration. In practice, STM manual therapy treatment parameters must be adjusted to deliver optimal mechanical stimuli to the tissue in order to elicit the desired response, including decreased pain; increased strength, mobility, function.

Impact of STM mechanotherapy on soft tissues

This perspective, although not exhaustive, will focus on the effects of STM mechanotherapy on soft tissues, including connective tissues, nerve, muscle, vascular and lymphatic tissues. STM intervention most likely has indirect, but significant effects on bone formation/resorption due to alterations in fluid flow and soft tissue adaptions leading to structural re-alignment, force re-distribution and ultimately bony adaptations; however, the reader is directed to other reviews that consider bone response with respect to mechanotherapies [11].

Connective tissue

Connective tissue, e.g. tendon, ligament, and fascia, is pervasive throughout the body and can be a source of dysfunction and pain for many people. Pre-clinical studies in animal models have shown STM to cause changes in connective tissue organization and biochemical properties. One study by Davidson et al. [37] found that rats with Achilles tendon injury treated with IASTM showed increased fibroblasts proliferation in the tendon compared to the control. This shows that STM altered the cells in the tendon inducing an increase in fibroblasts ultimately causing more collagen to be deposited. Another study by Gehlsen et al. [38] found IASTM at increasing pressures resulted in increased fibroblast proliferation, which may be related to improved healing. Loghmani and Warden [39] demonstrated IASTM improved biomechanical properties and collagen fiber organization in healing rat knee ligaments.

Case studies have also demonstrated positive clinical outcomes on connective tissue including knee [40], Achilles tendinopathy [41,42], De Quervain's tenosynovitis [43], and lateral epicondylosis [44,45]. Limited clinical trials are available, but those that are have found that STM improves outcomes in conditions involving connective tissue [5]. McCormack et al. [46] found in 2016 that STM administered via IASTM was more effective when combined with eccentric exercise than just eccentric exercise alone to treat Achilles tendinopathy.

Muscle tissue

Muscle is a highly mechanosensitive tissue that can be affected by and benefit from soft tissue mechanotherapy by decreasing recovery time after exercise, increasing muscle strength after application, counteracting the effects of aging, and facilitating appropriate healing after injury. Connective tissue, i.e. fascia, surrounds and pervades the muscle and muscle fibers; therefore, STM affects both the connective and muscle tissue. As described above, STM of the muscle-connective tissue complex has been shown to facilitate improved outcomes, including increased range of motion. STM has also been shown to immediately improve muscle function as indicated by an increase in force production after treatment [47-49]. Schillinger et al. [50] found participants that received STM had a quicker decrease in muscle enzymes indicative of muscle cell damage after a graded exercise test compared to a control. STM could decrease recovery time after exercise and increase muscle strength after application.

Other forms of soft tissue mechanotherapies have also demonstrated positive effects on muscle, suggesting the effects of STM on muscle tissue warrants greater investigation. For example, physical exercise provides forces to the muscle cell that causes change. In general, as a muscle contracts it puts a tensile and shear force on the cell and tensile load to the tissues. This causes a change in the nucleus and if the load is large enough, hypertrophy of the muscle fiber [51]. The hypertrophy then allows the muscle to produce increased force. Exercise is also used post-injury to help facilitate healing. After a muscle injury, a short rest phase is needed to allow the scar tissue to become stabilized followed by controlled loading which has been shown to improve alignment of the repairing myotubes and decrease the atrophy of the surrounding intact myotubes [52]. As another example, whole body vibration has recently been studied and found to stimulate improvements in muscle power to help counteract age and disease related changes in muscle function [53-55].

Nervous system tissue

Neurosensory stimulation provides information to an organism about its external and internal environment. Forces applied to soft tissue cause a change in the biochemical output of the cells producing a cascade of events resulting in a systemic effect. Analgesia, a temporary reduction or elimination of pain, is a reported benefit of STM interventions. STM may provide a form of counter-irritation (noxious stimulation) for pain modulation, thereby leading to an analgesic response. Blocked nocioception due to inhibition of pain signals via the gate-control mechanism is a possible explanation for its analgesic effects [56,57]. Subsequently, reduced pain can lead to muscle relaxation, which allows for normalized neuromuscular movement patterns and functional progression [7,58]. Pressure applied by STM may stimulate vagal activity, reduce stress hormones and decrease arousal leading to increased parasympathetic activity (e.g. decreased heart rate, blood pressure, respiratory rate) [7,59]. Soft tissue mechanotherapy can be effective in treating pain with resultant muscle relaxation.

Circulatory and lymphatic vessels

STM has been shown to have positive effects on vascularization and blood flow facilitating an improvement in and acceleration of healing. When soft tissue is mobilized, pressure is placed on the blood vessels. This mechanical stimulus has been shown to cause a mobilization of mast cells, macrophages and endothelial cells which are important in the formation of new vessels [60,61]. New vessel formation is important during the healing processes in order to ensure adequate blood supply to healing tissues. Higher skin temperature, which occurs during and after STM, theoretically means more blood flow to the area to remove waste and deliver nutrients. In a pre-clinical study by Loghmani and Warden [62], increased blood flow and arteriole sized capillaries were found in the region of IASTM-treated healing knee ligaments in rats as compared to contralateral controls. In another study by Okamoto [63], it was found that STM stimulated change of the cells in the arterial vessels causing a decrease in arterial stiffness and enhancing vascular endothelial function.

Manual lymph drainage is a specific STM technique that has been shown to help reduce edema associated with lymphedema, a chronic disease of fluid overload due to disruption of the lymph circulation [64,65]. In one study conducted on canines, manual lymphatic drainage was found to increase the flow of lymph into the thoracic duct and to increase the flow of leukocytes and other immune cells [66], which could potentially cause an increase in immune function [67]. The increase in lymph flow could be due to the formation of new lymph vessels as the lymph creates new pathways to drain the tissue. The increase in the movement of lymph has also been shown to decrease pain because of less pressure on surrounding soft tissue, increase the removal of waste products, and decrease edema.

Future Directions

The impact of STM on multiple tissue types is evident; however, more research is needed to take soft tissue mechanotherapy to the level of a STM prescription. The biological mechanisms underlying STM at the molecular, cellular and tissue levels and its effects on clinical outcomes need to be further investigated in studies ranging from pre-clinical animal models to randomized controlled clinical trials. The optimal type and timing of biophysical forces used during STM has not been adequately characterized in a clinically applicable manner [68];

thus, an essential step in understanding the underlying mechanobiology and optimizing STM treatment outcomes is the development of quantifiable STM (QSTM) approaches that can be used to administer STM in a realistic manner for clinical and research use. QSTM will facilitate a critical line of inquiry for completing STM dose pressure and frequency response studies that will better enable the exploration of soft tissue energetics and determination of optimal mechanical stimuli needed for tissue healing, repair and regeneration. The precise nature and complex interaction of cells within the ECM and mechanical forces should be further explored. Microscopic and macroscopic forces generated by STM intervention should be considered with respect to the interior and exterior of cells in all tissue types.

The impact of STM in various conditions and diseases needs to be better established. Since it is known that the cytoskeleton and nucleoplasm rigidity is altered with age [35], it is of particular import to explore the effects of STM on the mechanical integrity of aging cells and tissues in response to mechanical forces. The altered intrinsic mechanical compliance of aged cells disturbs their ability to sense and transduce mechanical signals, which consequently impairs cell function, e.g. altered migration, impaired healing and increased crosslinking, which can lead to fibrosis, cell degradation, genomic errors and chronic inflammation often associated with prevalent diseases, including musculoskeletal and neurological degenerative disorders, cardiovascular disease (e.g. "hardening of the arteries") and cancer [35,69]. STM may have significant implications in the prevention and treatment of cancer and metastasis since the rigidity of the ECM greatly impacts genomic stability and cell differentiation, function and migration [69]. STM also has a potential role in regenerative medicine since it may serve to facilitate endogenous reparative and regenerative pathways or used to augment exogenous procedures and regenerative cell therapy approaches. STM may indeed influence the activity and commitment of endogenous, tissue-resident adult stem and progenitor cells. Finally, the synergistic effects of STM in conjunction with surgical, pharmacological and other interventions, including exercise, therapeutic modalities and regenerative therapies, needs further research investigation.

Clinical Relevance

STM is a non-invasive, affordable and readily accessible form of mechanotherapy that is often used by clinicians to address a broad array of disorders. It doesn't just feel good, it does good. STM warrants rigorous scientific investigation and should be elevated to the level of a prescription, i.e. delivered at the optimal dose, pressure, and frequency to affect the desired molecular, cellular and tissue changes and outcomes.

Perhaps the value of this mechanotherapeutic modality, one that we literally have "in the palm of our hands," has been underestimated as a first line defense against soft tissue dysfunction, skeletal malalignment, pain and disease. This may be due to the difficulty in studying STM since there are a plethora of approaches that makes it challenging to standardize or compare outcomes. Perhaps it's also an unintended consequence of one of its benefits; the fact that STM is readily available and has been used since ancient times worldwide may have diminished its validity, relegating it as a rather commonplace, pedestrian, or even ill-refuted option. Nonetheless, STM is a powerful and direct form of mechanotherapy that has demonstrated effects on multiple systems and tissue types that can affect the function and structure of the individual as a whole through specific tissue-mediated changes.

Another benefit of STM is that it can be self-administered, empowering a patient to be proactive and accountable in regards to self-management of their pain and dysfunction, especially in combination with a targeted exercise program. Of even greater importance than determining its role in the management of disease or injury, is further establishing and validating the role of STM in the promotion of health and prevention of disease leading to significant healthcare cost reductions and improved quality of life in an aging population.

Conclusions

This perspective points to STM as a direct and potent form of mechanotherapy with positive impact on multiple tissue types. STM provides mechanical stimuli that through mechanotransduction mechanisms can lead to improved clinical outcomes. STM manual therapy should be approached as a precise prescription and a targeted force in physical therapies, rehabilitation, disease prevention and health promotions. Ongoing research is needed to further validate STM as a viable, non-invasive, cost-effective treatment option.

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